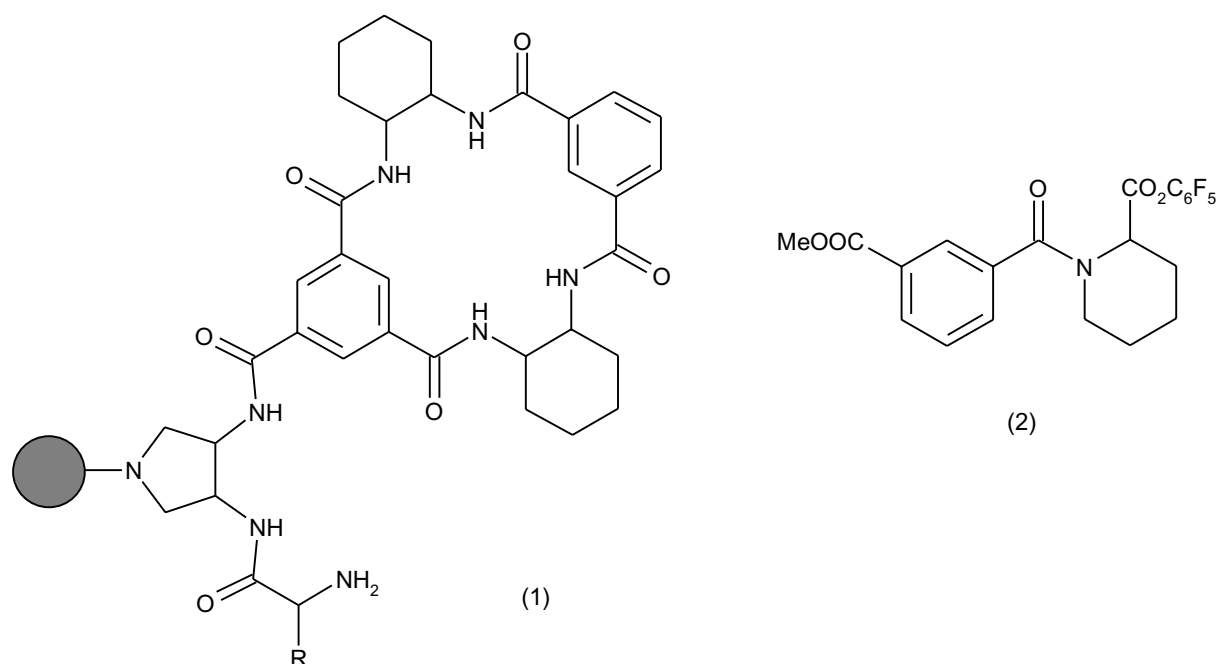


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Kinetic resolution by libraries

Ensuring that all chiral molecules are synthesised and tested as single enantiomers in biological systems is an essential requirement of modern drug discovery. Consequently, resolution of racemic materials, possibly using chiral HPLC, is often necessary to separate enantiomers. Combinatorial chemistry has recently been applied in the search for novel chiral selectors that will react enantiospecifically with racemic chemical compounds, specifically in this case, cyclic amino acid derivatives (M.D. Weingarten *et al.*, *J. Am. Chem. Soc.*, (1998), 120, 9112-9113).

Using Still's encoded split synthesis method on resin beads, a small library of 60 selector molecules (1) containing a chiral amine were prepared. The beads containing these molecules were incubated with a mixture of L- and D-proline pentafluorophenyl esters to investigate whether the library compounds would selectively pick out one of the two enantiomers by the formation of a new amide bond. To permit the recognition of beads that demonstrated such chiral discrimination, the two enantiomeric probe molecules were labelled with either a red or blue dye. Thus, if a bead contained a selector molecule that reacted enantiospecifically, it could be visually identified by a change of colour to red or blue. Beads that exhibited no such chiral discrimination would be stained brown as they will have reacted equally with both enantiomers.



Running the reaction and by picking the reddest and bluest beads, it was determined that resolution with enantiomeric excesses measured at 45-75% had been obtained. Subsequently, the preferred selector molecules were used in a kinetic resolution and filtration process to separate the enantiomers of related cyclic amino acid derivatives. Particular success with the homoproline (2) was reported in the paper, and there is every possibility of extending this methodology for the resolution of many other types of chiral molecule.

High loading single resin beads

The mix-and-split combinatorial method is a highly effective way of generating combinatorial libraries of huge size suitable for the discovery of novel pharmacologically active compounds. As the quantity of material available on each bead is often a limiting factor, considerable effort has been invested in finding novel polymer beads with high loading. One solution to this problem has been Bradley's method by which TentaGel beads can be derivatised with a dendrimer linker that allows significant increases in loading levels.

A recent publication from Bradley's group describes the ability of these high-loading beads to generate sufficient material for full structural analysis (N.J. Wells *et al.*, *J. Org. Chem.*, (1998), 63, 6430-6431). The peptide Fmoc-Val-Phe-Ala-OH was prepared using standard peptide coupling conditions on the HMP linker. Sufficient material was available from one resin bead to permit 500 MHz NMR by *in situ* cleavage of the peptide in the NMR tube using 1% F₃CCOOD in deuteriochloroform. HPLC analysis revealed that approximately 32 nmol of essentially pure material had been prepared.

In a separate experiment a small library of 20 leu-enkephalin analogues were prepared and analysed by HPLC and ESMS, demonstrating the robustness and versatility of these high-loading beads. One additional comment made in the paper was that chemical derivatisation of the dendrimer derivatised material generally proceeded rapidly and under nonforcing conditions.